REMARKS

Claims 88-107 were originally pending in this application. As a result of a restriction requirement mailed on July 7, 2010, claims 88-95 were elected. In response to an Office Action mailed September 16, 2010 claims 88 and 94 were been amended, claims 89-93 and 95 were been canceled, claims 108 – 113 were added and claims 110-113 were presumed withdrawn as directed to a non-elected invention. Claims 88, 94, 108-109 are currently pending.

Rejections under 35 U.S.C. §112, first paragraph:

Written Description

The Office Action states that claims 88, 94, 108 and 109 are rejected as failing to meet the written description requirement due to the claims containing subject matter that was not described in the specification in such a way as to reasonably convey to one of skill in the relevant art that, at the time of filing, the inventor had possession of the claimed invention. Specifically, the Office Action states that the Examiner could not "identify a disclosure of either a vaccine composition or methods of vaccination utilizing the combination of a polyhydroxylated pyrrolizidine alkaloid, such as casuarine, a neoantigen, and a TLR ligand."

In establishing a disclosure, an applicant may rely not only on the description and drawing as filed, but also on the original claims. *See* MPEP 608.01(l). The Examiner is directed to original claim 12, which reads : "The method of claim 3(g) wherein the immunotherapy further comprises: (a) the co-administration of an antigen (e.g. a neoantigen), which is optionally targeted to endogenous dendritic cells (e.g. present in the exosome); and/or (b) the co-administration of a dendritic cell maturation stimulant. Claim 3(g), from which claim 12 depends, may depend from claim 1 or claim 2 and includes a method of using an alkaloid in a vaccine. Thus, original claim 12 includes the elements of an alkaloid, a neoantigen and a dendritic cell maturation stimulant as a part of the original disclosure.

Regarding the limitation of a polyhydroxylated pyrrolizidine alkaloid, page 23 of the specification as filed provides, under the section "Alkaloids for Use According to the Invention," ample support for the use of a polyhydroxylated pyrrolizidine alkaloid in the present invention,

including original claim 12. Specifically, lines 29-33 state "Particularly preferred are alkaloids selected from the following classes…(d) pyrrolizidine alkaloids" and line 40 states "The alkaloid may be polyhydroxylated."

Regarding the limitation of a neoantigen, Claim 12 itself recites the use of a neoantigen, and the specification ample support for the use of neoantigens in aspects of the invention including in vaccines (see pages 17 and 38, and numerous original claims).

Regarding the limitation of TLR ligands, applicant respectfully asserts that ample support for this limitation exists in the application as filed. Specifically, claim 12 recites a "dendritic cell maturation stimulant". As was pointed out in the Office Action, the specification as filed describes the use of TLR-ligands, such as lipopolysaccharide (LPS) or monophosphoryl lipids, as dendritic cell maturation agents. *See* pages 17 and 31 of the specification as filed. Accordingly, each of the elements of 1) a polyhydroxylated pyrrolizidine alkaloid, 2) a neoantigen, and 3) a TLR-ligand are all amply supported in the specification as filed. For the above reasons, Applicants respectfully assert that the presently pending claims do meet the requirements of 35 U.S.C. §112 and Applicants request that the written description/new matter rejection be withdrawn.

Rejections under 35 U.S.C. §103:

The Office Action states that claims 88, 94, 108 and 109 are rejected under 35 U.S.C. §103(a) as unpatentable over Shizuo Akira, *Mammalian Toll-Like Receptors*, 15 CURR. OPIN. IMMUNOL. 5, 8, 9 (February 2003) (hereinafter "Akira"), in view of Ruain Xu et al., *Molecular Therapeutics of HBV*, 3 CURR. GENE THERAPY 341 (2003) (hereinafter "Xu"), Alison Watson et al., *Polyhydroxylated Alkaloids – Natural Occurrence and Therapeutic Applications*, 56 PHYTOCHEM. 265 (2001) (hereinafter "Watson"), as evidenced by Andrew Bell et al., *Synthesis of Casuarines [Pentahydroxylated Pyrrolizidines] by Sodium Hydrogen Telluride-Induced Cyclisations of Azidodimesylates*, 38 TET. LET. 5869 (1997) (hereinafter "Bell") as put forth in the previous Office Action, and in further view of Guity Ghaffari et al., *Human Lymphocyte Proliferation Responses Following Primary Immunization with Rabies Vaccine as Neoantigen*, 8 CLIN. DIAG. LAB. IMMUNOL. 880 (2001) (hereinafter "Ghaffari").

The present Office Action states that the Akira, Xu, Watson and Bell references are being applied as described in the previous Office Action (see page 6 of the Office Action). The following arguments are made with those interpretations of the references in mind.

With regard to the Akira reference, the previous Office Action stated that this reference "indicates that exposing immune systems to certain bacterial, fungal, and viral TLR ligands would induce an immune response by promoting the production of cytokines and other cellular signaling media." As also pointed out in the Office Action, Akira fails to "discuss or provide a rationale for combining immunotherapy directed to bacterial, fungal, or viral infections by administering a combination of a TLR ligand and a polyhydroxylated alkaloid." Akira is focused on the specific nature of particular toll-like receptors and their evolutionary development, with some mention of known or suspected signal transduction pathways. The discussion in Akira is not of particular relevance to the presently claimed invention and there is no motivation to combine this reference with any of the other cited references to arrive at the presently claimed invention. Additionally, stimulation of IL-2 production by dendritic cells is not discussed or even hinted at in Akira, in fact, IL-2 itself is not mentioned or implicated in the Akira reference. Further, Akira does not discuss or provide a rationale for combining a polyhydroxylated pyrrolizidine alkaloid, a neoantigen, and a toll-like receptor ligand to vaccinate a patient, as required by the present claims. Neither does Akira discuss or imply that the release of IL-2 from dendritic cells would be the result of such a combination of elements.

The previous Office Action stated that the Xu reference "describes a variety of approaches to promoting improved immunotherapy, including not only direct antiviral strategies, but also the modulation of the immune system of the subject to be treated." However, the Xu reference is focused on the use of gene therapy as a way to stimulate production of endogenous immune material and this is not relevant to the present amended claims, which include no gene therapies. Further, nothing in Xu remedies the deficiencies found in Akira, namely, there is no indication that use of a polyhydroxylated pyrrolizidine alkaloid, a neoantigen and a toll-like receptor ligand would result in a prolonged and pronounced stimulation of IL-2 production in the dendritic cells of a patient nor is there any indication of the desirability of using this combination of compounds in a method of vaccination. Indeed, the Xu reference emphasizes the need for gene therapy techniques in making certain known molecular agents therapeutically effective.

(*see* Xu et al., page 345: "[s]ince systemic application of cytokines is associated with severe side effects, researches on targeted delivery or endogenetic expression through a gene therapy approach, have been prompted" (sic)). As a result, if anything, the Xu reference teaches away from using the present invention without the concurrent use of gene therapy techniques, such as for delivery.

The previous Office Action further stated that the Watson reference indicates "that a variety of polyhydroxylated alkaloids, including casuarine and swainsonine, act as potent, reversible, and competitive glycosidase inhibitors" and that "owing to this activity, polyhydroxylated alkaloids such as casuarine would find utility as immune-stimulants, anti-viral agents, and general anti-infective agents". The Office Action also stated that the Bell reference echoes the findings of Watson, with regard to casuarine's activity as an inhibitor of glycosidases and glucosidase I in particular. With respect to the Watson and Bell references, neither reference remedies the deficiencies of both Akira and Xu with respect to the presently claimed invention. Specifically, neither Watson nor Bell teach vaccination of a patient through the use of a polyhydroxylated pyrrolizidine alkaloid along with a neoantigen and a toll-like receptor ligand wherein IL-2 production is stimulated in the dendritic cells of the patient. Characterization of some polyhydroxylated alkaloids as glycosidase inhibitors provides no indication of their use as vaccinating agents capable of inducing IL-2 production from dendritic cells when co-administered with a neoantigen and a toll-like receptor ligand.

Additionally, the premise that Watson teaches that polyhydroxylated alkaloids are desirable as immune stimulants is very questionable. Watson's disclosure, as relevant to polyhydroxylated alkaloids possibly being desirable immune stimulants, is limited to three studies and three circumstances. The first study showed that the administration of swainsonine decreased the lethality of cytotoxic anticancer agents, but the effect was highly variable and volatile (see Watson et al., page 283 "…these responses were critically dependent on the dose, sequence and timing of swainsonine administration."). The second study examined the protective effects of swainsonine when used to protect cells from cyclophosphamide or azido-3'-deoxythymidine (AZT). The author concluded that swainsonine protected cells from AZT toxicity, and that "the possibility exists that swainsonine could be used to accelerate the recovery of bone marrow cellularity and competence following following high-dose chemotherapy or

autologous bone marrow transplantation, or as an adjuvant during AZT treatment." The third study referenced in Watson et al. is a one sentence reference to a study by Kayakiri et al. saying nectrisine "has been reported to restore the immune response of immune suppressed mice."

The Bell reference focuses on the chemical synthesis of casuarines. It mentions in the opening paragraph that casuarine inhibits glycosidases and has been used as an anticancer agent in Western Samoa. Bell also notes that it is found in the leaves of plants used to treat diabetes in India and AIDS in Africa.

The present Office Action cites Ghaffari et al. as disclosing "the use of viral rabies vaccine as a neoantigen for the vaccination of individuals against rabies infection" and thus teaches the introduction of a neoantigen as a part of an immune therapy (see Office Action page 6). Ghaffari et al. is a study of the proliferation of T-cells in patients exposed to the rabies virus for the first time. The purpose of this study was to assess the specific proliferation patterns of T-cells in response to exposure to the rabies vaccine as an antigen, and not to alter or enhance the immune response at all (see Ghaffari et al., page 882-883). This calls into question any motivation to combine Ghaffari et al with Akira, Xu, Watson or Bell, as the only addition Ghaffari et al. makes to the disclosures of these references is that when exposed to a rabies vaccine for the first time, T-cells may proliferate. Ultimately, Ghaffari et al. does not teach anything about small molecule neoantigens. The fact that T-cells may proliferate in response to an antigen is a foundation of immunology and does not remedy any of the deficiencies pointed out above for the other references.

In summary, the cited references of Akira, Xu, Watson, Bell, and Ghaffari do not provide teachings sufficient to render the presently claimed invention obvious under 35 U.S.C. §103(a). Applicants claims relate to the vaccination of a patient using a combination of a polyhydroxylated pyrrolizidine alkaloid along with a neoantigen and a toll-like receptor ligand wherein the production of IL-2 in the dendritic cells is stimulated in the patient. The references cited in the Office Action do not combine to render the present invention obvious. At most, the references show that certain polyhydroxylated alkaloids may have an impact on the immune system and that the introduction of antigens may stimulate immune system activity. Thus, there has been no prima facie case of obviousness established by the combination of Akira, Xu, Watson, Bell and Ghaffari.

Further, even if each element of the presently claimed invention was shown by the above references, "[o]bviousness requires more than a mere showing that the prior art includes separate references covering each separate limitation in a claim under examination." *Unigene Laboratories, Inc. v. Apotex, Inc.*, 99 U.S.P.Q.2d 1858, 1871 (*citing KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 418 (2007). "Rather, obviousness requires the additional showing that a person of ordinary skill at the time of the invention would have selected and combined those prior art elements in the normal course of research and development to yield the claimed invention." *Id.* As described above, even if the references cited in the Office Action did cover each separate limitation of the presently claimed invention, a person of ordinary skill at the time of the invention would not have selected and combined the prior art elements as proposed by the Office Action not least because the references themselves suggest that they not be combined. For example, Xu suggests gene therapy, not small molecule stimulation and the thrust of Ghaffari was not toward small molecule immune stimulation, but rather toward rabies antigen. For these reasons, Applicants respectfully assert that the presently outstanding rejection under 35 U.S.C. §103(a) is inapposite with regard to the presently pending claims.

As a result of the above discussion, Applicant respectfully requests that the rejection under 35 U.S.C. §103(a) be withdrawn with respect to the currently pending claims.

Double Patenting:

The Office Action stated that claims 88, 94, 108 and 109 are provisionally rejected on the grounds of non-statutory double patenting over two copending applications 1) 10/597,296, and 2) 10/543,014. As stated in the Office Action, a timely filed Terminal Disclaimer may be used to obviate such rejections. Applicants note the provisional nature of these rejections and will address them, if appropriate, at a time when one or both of the copending applications issue.

CONCLUSION

It is believed that the application is in condition for allowance, and such action is respectfully requested.

If a telephone conference would be of assistance in advancing prosecution of the subject application, the Examiner is invited to telephone the undersigned attorney at the telephone number provided.

Respectfully submitted,

Brian Reese

Brian E. Reese, Esq.
Attorney for Applicant(s)
Registration No. 64,538

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HESLIN ROTHENBERG FARLEY & MESITI, P.C.
5 Columbia Circle
Albany, New York 12203
Telephone: (518) 452-5600
Facsimile: (518) 452-5579